OIPE JC182
SEP 0 3 2003
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Title: IDENTIFICATION OF THE GENE CAUSING THE MOUSE SCURFY PHENOTYPE AND ITS HUMAN ORTHOLOG
Express Mail No. EV336613357US
Inventor(s): Mary E. Brunkow et al.   Serial No. 09/696,867   Docket No. 240083.501D6

MOUSE *Fkh*^{sf} cDNA SEQUENCE

```
   1  GCTGATCCCC CTCTAGCAGT CCACTTCACC AAGGTGAGCG AGTGTCCCTG
  51  CTCTCCCCCA CCAGACACAG CTCTGCTGGC GAAAGTGGCA GAGAGGTATT
 101  GAGGGTGGGT GTCAGGAGCC CACCAGTACA GCTGGAAACA CCCAGCCACT
 151  CCAGCTCCCG GCAACTTCTC CTGACTCTGC CTTCAGACGA GACTTGGAAG
 201  ACAGTCACAT CTCAGCAGCT CCTCTGCCGT TATCCAGCCT GCCTCTGACA
 251  AGAACCCAAT GCCCAACCCT AGGCCAGCCA AGCCTATGGC TCCTTCCTTG
 301  GCCCTTGGCC CATCCCCAGG AGTCTTGCCA AGCTGGAAGA CTGCACCCAA
 351  GGGCTCAGAA CTTCTAGGGA CCAGGGGCTC TGGGGGACCC TTCCAAGGTC
 401  GGGACCTGCG AAGTGGGGCC CACACCTCTT CTTCCTTGAA CCCCCTGCCA
 451  CCATCCCAGC TGCAGCTGCC TACAGTGCCC CTAGTCATGG TGGCACCGTC
 501  TGGGGCCCGA CTAGGTCCCT CACCCCACCT ACAGGCCCTT CTCCAGGACA
 551  GACCACACTT CATGCATCAG CTCTCCACTG TGGATGCCCA TGCCCAGACC
 601  CCTGTGCTCC AAGTGCGTCC ACTGGACAAC CCAGCCATGA TCAGCCTCCC
 651  ACCACCTTCT GCTGCCACTG GGGTCTTCTC CCTCAAGGCC CGGCCTGGCC
 701  TGCCACCTGG GATCAATGTG GCCAGTCTGG AATGGGTGTC CAGGGAGCCA
 751  GCTCTACTCT GCACCTTCCC ACGCTCGGGT ACACCCAGGA AAGACAGCAA
 801  CCTTTTGGCT GCACCCCAAG GATCCTACCC ACTGCTGGCA AATGGAGTCT
 851  GCAAGTGGCC TGGTTGTGAG AAGGTCTTCG AGGAGCCAGA AGAGTTTCTC
 901  AAGCACTGCC AAGCAGATCA TCTCCTGGAT GAGAAAGGCA AGGCCCAGTG
 951  CCTCCTCCAG AGAGAAGTGG TGCAGTCTCT GGAGCAGCAG CTGGAGCTGG
1001  AAAAGGAGAA GCTGGGAGCT ATGCAGGCCC ACCTGGCTGG GAAGATGGCG
1051  CTGGCCAAGG CTCCATCTGT GGCCTCAATG GACAAGAGCT CTTGCTGCAT
1101  CGTAGCCACC AGTACTCAGG GCAGTGTGCT CCCGGCCTGG TCTGCTCCTC
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Fig. 1A

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1151  GGGAGGCTCC AGACGGCGGC CTGTTTGCAG TGCGGAGGCA CCTCTGGGGA
1201  AGCCATGGCA ATAGTTCCTT CCCAGAGTTC TTCCACAACA TGGACTACTT
1251  CAAGTACCAC AATATGCGAC CCCCTTTCAC CTATGCCACC CTTATCCGAT
1301  GGGCCATCCT GGAAGCCCCG GAGAGGCAGA GGACACTCAA TGAAATCTAC
1351  CATTGGTTTA CTCGCATGTT CGCCTACTTC AGAAACCACC CCGCCACCTG
1401  GAAGAATGCC ATCCGCCACA ACCTGAGCCT GCACAAGTGC TTTGTGCGAG
1451  TGGAGAGCGA GAAGGGAGCA GTGTGGACCG TAGATGAATT TGAGTTTCGC
1501  AAGAAGAGGA GCCAACGCCC CAACAAGTGC TCCAATCCCT GCCCTTGACC
1551  TCAAAACCAA GAAAAGGTGG GCGGGGGAGG GGGCCAAAAC CATGAGACTG
1601  AGGCTGTGGG GGCAAGGAGG CAAGTCCTAC GTGTACCTAT GGAAACCGGG
1651  CGATGATGTG CCTGCTATCA GGGCCTCTGC TCCCTATCTA GCTGCCCTCC
1701  TAGATCATAT CATCTGCCTT ACAGCTGAGA GGGGTGCCAA TCCCAGCCTA
1751  GCCCCTAGTT CCAACCTAGC CCCAAGATGA ACTTTCCAGT CAAAGAGCCC
1801  TCACAACCAG CTATACATAT CTGCCTTGGC CACTGCCAAG CAGAAAGATG
1851  ACAGACACCA TCCTAATATT TACTCAACCC AAACCCTAAA ACATGAAGAG
1901  CCTGCCTTGG TACATTCGTG AACTTTCAAA GTTAGTCATG CAGTCACACA
1951  TGACTGCAGT CCTACTGACT CACACCCCAA AGCACTCACC CACAACATCT
2001  GGAACCACGG GCACTATCAC ACATAGGTGT ATATACAGAC CCTTACACAG
2051  CAACAGCACT GGAACCTTCA CAATTACATC CCCCCAAACC ACACAGGCAT
2101  AACTGATCAT ACGCAGCCTC AAGCAATGCC CAAAATACAA GTCAGACACA
2151  GCTTGTCAGA
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Fig. 1B

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MOUSE Fkh^{sf} PROTEIN SEQUENCE

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  1  MPNPRPAKPM APSLALGPSP GVLPSWKTAP KGSELLGTRG SGGPFQGRDL
 51  RSGAHTSSSL NPLPPSQLQL PTVPLVMVAP SGARLGPSPH LQALLQDRPH
101  FMHQLSTVDA HAQTPVLQVR PLDNPAMISL PPPSAATGVF SLKARPGLPP
151  GINVASLEWV SREPALLCTF PRSGTPRKDS NLLAAPQGSY PLLANGVCKW
201  PGCEKVFEEP EEFLKHCQAD HLLDEKGKAQ CLLQREVVQS LEQQLELEKE
251  KLGAMQAHLA GKMALAKAPS VASMDKSSCC IVATSTQGSV LPAWSAPREA
301  PDGGLFAVRR HLWGSHGNSS FPEFFHNMDY FKYHNMRPPF TYATLIRWAI
351  LEAPERQRTL NEIYHWFTRM FAYFRNHPAT WKNAIRHNLS LHKCFVRVES
401  EKGAVWTVDE FEFRKKRSQR PNKCSNPCP*
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Fig. 2

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HUMAN *FKH*^{sf} cDNA Sequence

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   1  GCACACACTC ATCGAAAAAA ATTTGGATTA TTAGAAGAGA GAGGTCTGCG
  51  GCTTCCACAC CGTACAGCGT GGTTTTTCTT CTCGGTATAA AAGCAAAGTT
 101  GTTTTTGATA CGTGACAGTT TCCCACAAGC CAGGCTGATC CTTTTCTGTC
 151  AGTCCACTTC ACCAAGCCTG CCCTTGGACA AGGACCCGAT GCCCAACCCC
 201  AGGCCTGGCA AGCCCTCGGC CCCTTCCTTG GCCCTTGGCC CATCCCCAGG
 251  AGCCTCGCCC AGCTGGAGGG CTGCACCCAA AGCCTCAGAC CTGCTGGGGG
 301  CCCGGGGCCC AGGGGGAACC TTCCAGGGCC GAGATCTTCG AGGCGGGGCC
 351  CATGCCTCCT CTTCTTCCTT GAACCCCATG CCACCATCGC AGCTGCAGCT
 401  GCCCACACTG CCCCTAGTCA TGGTGGCACC CTCCGGGGCA CGGCTGGGCC
 451  CCTTGCCCCA CTTACAGGCA CTCCTCCAGG ACAGGCCACA TTTCATGCAC
 501  CAGCTCTCAA CGGTGGATGC CCACGCCCGG ACCCCTGTGC TGCAGGTGCA
 551  CCCCCTGGAG AGCCCAGCCA TGATCAGCCT CACACCACCC ACCACCGCCA
 601  CTGGGGTCTT CTCCCTCAAG GCCCGGCCTG GCCTCCCACC TGGGATCAAC
 651  GTGGCCAGCC TGGAATGGGT GTCCAGGGAG CCGGCACTGC TCTGCACCTT
 701  CCCAAATCCC AGTGCACCCA GGAAGGACAG CACCCTTTCG GCTGTGCCCC
 751  AGAGCTCCTA CCCACTGCTG GCAAATGGTG TCTGCAAGTG GCCCGGATGT
 801  GAGAAGGTCT TCGAAGAGCC AGAGGACTTC CTCAAGCACT GCCAGGCGGA
 851  CCATCTTCTG GATGAGAAGG GCAGGGCACA ATGTCTCCTC CAGAGAGAGA
 901  TGGTACAGTC TCTGGAGCAG CAGCTGGTGC TGGAGAAGGA GAAGCTGAGT
 951  GCCATGCAGG CCCACCTGGC TGGGAAAATG GCACTGACCA AGGCTTCATC
1001  TGTGGCATCA TCCGACAAGG GCTCCTGCTG CATCGTAGCT GCTGGCAGCC
1051  AAGGCCCTGT CGTCCCAGCC TGGTCTGGCC CCCGGGAGGC CCCTGACAGC
1101  CTGTTTGCTG TCCGGAGGCA CCTGTGGGGT AGCCATGGAA ACAGCACATT
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Fig. 3A

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1151  CCCAGAGTTC CTCCACAACA TGGACTACTT CAAGTTCCAC AACATGCGAC
1201  CCCCTTTCAC CTACGCCACG CTCATCCGCT GGGCCATCCT GGAGGCTCCA
1251  GAGAAGCAGC GGACACTCAA TGAGATCTAC CACTGGTTCA CACGCATGTT
1301  TGCCTTCTTC AGAAACCATC CTGCCACCTG GAAGAACGCC ATCCGCCACA
1351  ACCTGAGTCT GCACAAGTGC TTTGTGCGGG TGGAGAGCGA GAAGGGGGCT
1401  GTGTGGACCG TGGATGAGCT GGAGTTCCGC AAGAAACGGA GCCAGAGGCC
1451  CAGCAGGTGT TCCAACCCTA CACCTGGCCC CTGACCTCAA GATCAAGGAA
1501  AGGAGGATGG ACGAACAGGG GCCAAACTGG TGGGAGGCAG AGGTGGTGGG
1551  GGCAGGGATG ATAGGCCCTG GATGTGCCCA CAGGGACCAA GAAGTGAGGT
1601  TTCCACTGTC TTGCCTGCCA GGGCCCCTGT TCCCCCGCTG GCAGCCACCC
1651  CCTCCCCCAT CATATCCTTT GCCCCAAGGC TGCTCAGAGG GGCCCCGGTC
1701  CTGGCCCCAG CCCCCACCTC CGCCCCAGAC ACACCCCCCA GTCGAGCCCT
1751  GCAGCCAAAC AGAGCCTTCA CAACCAGCCA CACAGAGCCT GCCTCAGCTG
1801  CTCGCACAGA TTACTTCAGG GCTGGAAAAG TCACACAGAC ACACAAAATG
1851  TCACAATCCT GTCCCTCAC
```

Fig. 3B

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HUMAN FKH^{sf} PROTEIN SEQUENCE

```
  1  MPNPRPGKPS APSLALGPSP GASPSWRAAP KASDLLGARG PGGTFQGRDL
 51  RGGAHASSSS LNPMPPSQLQ LPTLPLVMVA PSGARLGPLP HLQALLQDRP
101  HFMHQLSTVD AHARTPVLQV HPLESPAMIS LTPPTTATGV FSLKARPGLP
151  PGINVASLEW VSREPALLCT FPNPSAPRKD STLSAVPQSS YPLLANGVCK
201  WPGCEKVFEE PEDFLKHCQA DHLLDEKGRA QCLLQREMVQ SLEQQLVLEK
251  EKLSAMQAHL AGKMALTKAS SVASSDKGSC CIVAAGSQGP VVPAWSGPRE
301  APDSLFAVRR HLWGSHGNST FPEFLHNMDY FKFHNMRPPF TYATLIRWAI
351  LEAPEKQRTL NEIYHWFTRM FAFFRNHPAT WKNAIRHNLS LHKCFVRVES
401  EKGAVWTVDE LEFRKKRSQR PSRCSNPTPG P*
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Fig. 4

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Vector for generation of FKH^{sf} Transgenic mice

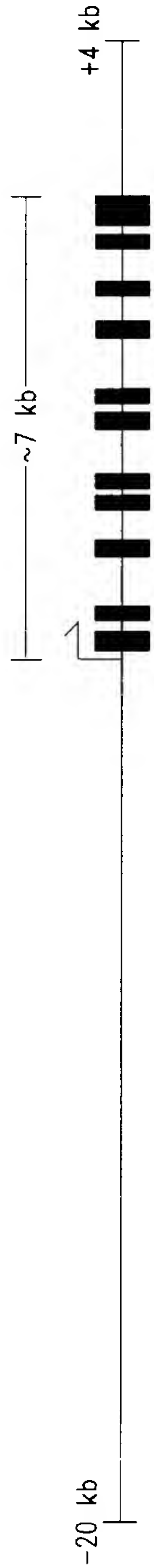

Fig. 5

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FKHsf Transgene corrects the defect in scurfy animals

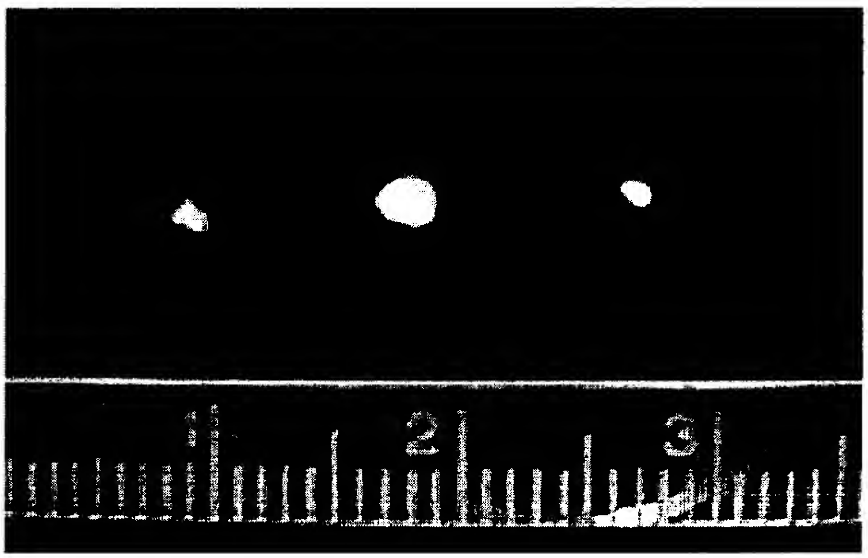

Fig. 6

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FKHsf tg mice have reduce lymph node cells compared to normal cells

Cell number	Mouse genotype Normal	Scurfy	Transgenic
Cells / LN	0.92	1.97	0.29
Cells / Thymus	0.76	0.54	0.76

Fig. 7

FKHsf trangenic mice respond poorly to in vitro stimulation

Proliferation	Mouse genotype Normal	Scurfy	Transgenic
No stimulation	778	23488	596
Anti-CD3+Anti-CD28	22932	225981	9106

Fig. 8

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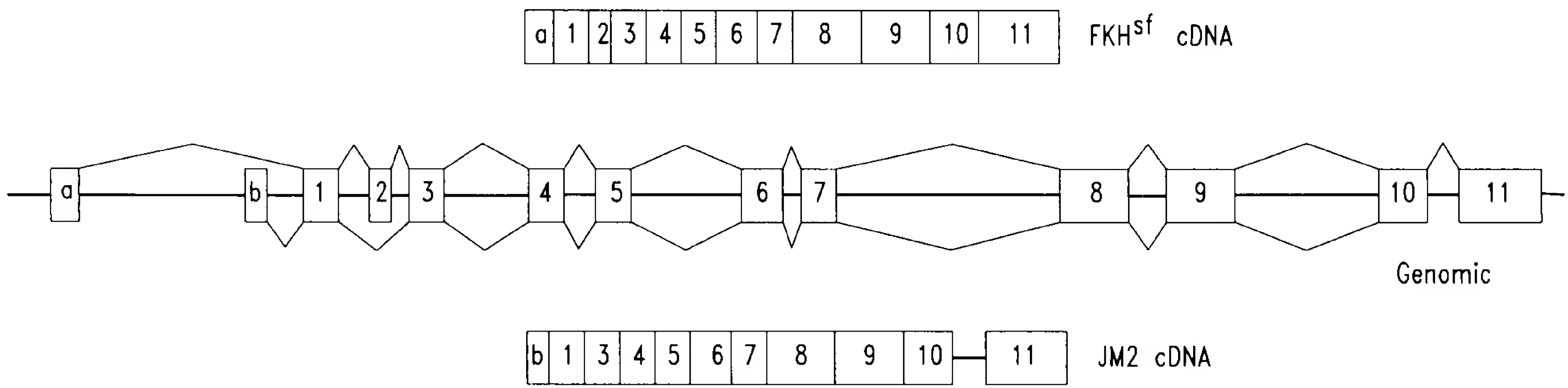

Comparison of FKH^{sf} and JM2 c DNAs. Exon/intron structure is shown (Genomic) as open rectangles (exons) joined by heavy horizontal lines (introns). Coding exons are numbered 1-11 as determined by sequence analysis of FKH^{sf} cDNA; non-coding 5' exons are labelled *a* and *b*. The FKH^{sf}-specific and JM2-specific splicing patterns and resulting cDNAs are indicated above and below the genomic structure, respectively.

Fig. 9

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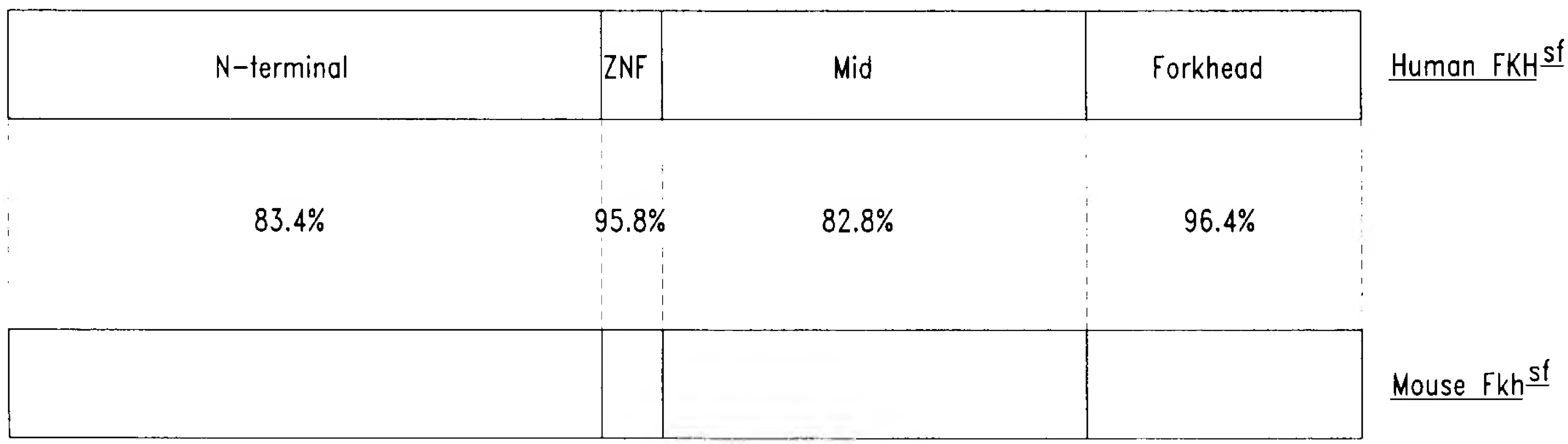

Human and mouse FKH^{sf} proteins are highly conserved.

Fig. 10